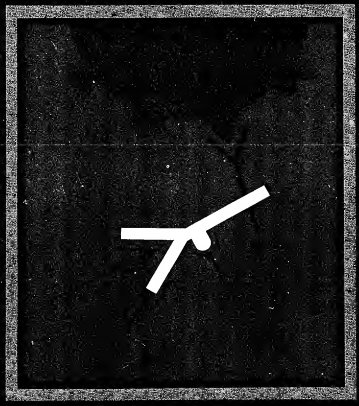
Stewart Sell

Basic Immunology

Immune Mechanisms in Health and Disease



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6 Antibodies, Immunoglobulins, and Receptors

Antibodies belong to a group of structurally related glycoprotein molecules found in the blood and extracellular fluids and known collectively as immunoglobulins. Immunoglobulins are the products of plasma cells, which secrete these proteins into serum and tissue fluids. Each plasma cell synthesizes and secretes large numbers of a single antibody that has the same antigen-binding specificity. Whereas some immunoglobulins are produced at all times in most normal animals, specific antibodies are a unique subset of immunoglobulins produced in response to antigenic stimulation. Given the enormous number of antigen specificities (epitopes) identifiable, an individual must have the ability to produce a great variety of antibody molecules. Cell surface antibodies on B cells serve as specific receptors for antigen; T cells also bear receptor molecules similar to antibodies, but having different structural components.

Gamma Globulin

The first identification of antibodies among the serum proteins was accomplished by electrophoresis in 1938 (Fig. 6-1). It was

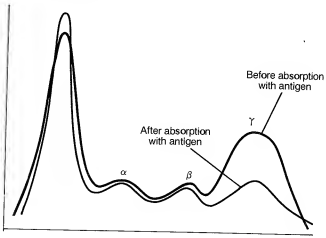

Figure 6-1. If serum is placed under an electric gradient, the proteins will migrate in the charged field produced. The solid line depicts the serum protein electrophoresis pattern produced after absorption of serum from a hyperimmunized animal with the immunizing antigen. The dotted line depicts the protein pattern before absorption. It was thus shown that antibodies are largely found in the gamma globulins (the least negatively charged serum proteins).

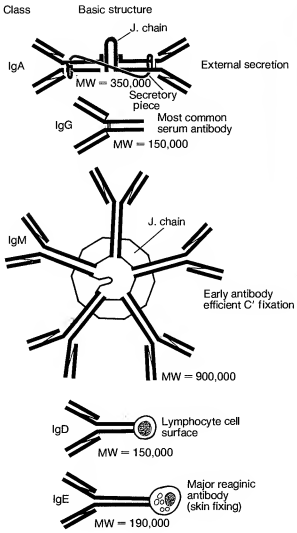

Figure 6-2. Human immunoglobulin classes. Human humoral (circulating) antibodies belong to five classes: IgA, IgG, IgM, IgD, and IgE. The basic unit of each immunoglobulin molecule consists of two pairs of polypeptide chains joined by disulfide bonds. All immunoglobulins have the same L (light)-chain components, identifiable antigenically as kappa (κ) or lambda (λ), with any given immunoglobulin molecule having two κ-chains or two λ-chains. No naturally occurring immunoglobulin molecule has one κ-chain and one λ-chain. H (heavy)-chains of each immunoglobulin class are unique for that class and determine its biologic properties. H-chains of each immunoglobulin class are designated by the Greek letter corresponding to the capital letter identifying the class.

Biological Properties of Immunoglobulins

The five classes of immunoglobulins have different biological properties and are distributed differently in the intact animal. The structure responsible for the biological properties of each immunoglobulin class is located on that part of the immunoglobulin molecule that is unique for each class (the Fc portion of the H-chain).

Each IgG molecule consists of one H_2L_2 unit with a molecular weight of about 140,000. Molecules of the IgG class are actively transported across the placenta and provide passive immunity to the newborn infant at a time when the infant's immune mechanisms are not developed. IgG is widely distributed in the tissue fluids and is about equally divided between the intravascular and extravascular spaces.

IgM is the first immunoglobulin class produced by the

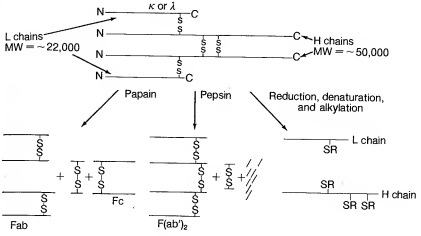

Figure 6-3. Human immunoglobulin fragments. The intact IgG molecule may be fragmented by different reagents into subunits. Digestion with papain occurs on the amino side of the interchain disulfide bond and results in three major fragments, two Fab and one Fc, and a minor fragment. Fab fragments consist of an L-chain and the amino half of an H-chain joined by a disulfide bond. The Fc fragment consists of the carboxy halves of H-chains joined by a disulfide bond. An additional small peptide from the middle of the heavy chains containing a disulfide bond is also produced. The Fab fragment contains an antigen-binding site and reacts with, but does not precipitate, antigen because it is monovalent. The Fc portion is responsible for biological properties such as complement fixation. Digestion with pepsin occurs on the carboxy side of the interchain disulfide bond and results in two F(ab') fragments joined by a disulfide bond because one of the disulfide bonds joining the H-chains is preserved. This fragment, $F(ab')_2$, reacts with and precipitates antigen because it is divalent (contains two antigen-binding sites). Additional peptide fragments, some containing disulfide bonds, are produced by the action of pepsin, presumably due to further digestion of the Fc fragment. Reduction of disulfide bonds, alkylation of free SH groups ($R = CH_2CONH_2$), and denaturation of ionic and hydrogen bonds result in liberation of polypeptide chains— two L-chains (MW 22,000) and two H-chains (MW 50,000). Each polypeptide chain contributes to the antigen-binding site of the intact Fab fragment. That portion of H-chain present in the Fab fragment is called the Fd piece.

maturing fetus and may be the first immunoglobulin class representing a given antibody specificity following immunization (primary response). IgM occurs as five H_2L_2 units joined to each other by disulfide bonds located on the Fc part of the molecule and to the J-chain; its molecular weight is 900,000. IgM is found mainly in the intravascular fluids (80%). It is also the most efficient class of immunoglobulin in fixing complement and therefore is highly active in cytotoxic and cytolytic reactions.

IgM does not normally cross the placenta from mother to fetus, but may be produced actively by the fetus prior to birth, especially if the fetus has been exposed to antigens by infection. Thus IgM antibodies in the cord blood of the fetus are evidence of fetal immunization by exposure to infectious agents.